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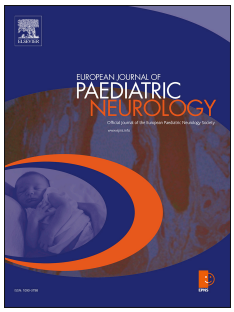

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Development of muscle tone impairments in high-risk infants: associations with cerebral palsy and cystic periventricular leukomalacia

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Abstract

Aim: To assess the prevalence and development of muscle tone impairments in infants at high risk of developmental disorders, and their associations with cerebral palsy (CP) and cystic periventricular leukomalacia (cPVL).

Method: Longitudinal exploration of muscle tone in 39 infants at high risk of CP (LEARN2MOVE 0-2 project) mostly due to an early lesion of the brain. Muscle tone was assessed ≥4 times between 0-21 months corrected age (CA) with the Touwen Infant Neurological Examination. Diagnosis of CP was determined at 21 months CA. Neonatal neuro-imaging was available. Developmental trajectories were calculated using generalized linear mixed effect models.

Results: Infants showed atypical muscle tone in three or four body parts in 93% (172/185) of the assessments. The most prevalent muscle tone pattern was hypotonia of neck and trunk with hypertonia of the limbs (28%). From 7 months CA onwards hypertonia of the arms was associated with CP. Asymmetric arm tone during infancy was associated with unilateral CP. At 18-21 months CA ankle hypertonia was associated with CP at 21 months; leg hypertonia in infancy was not associated with CP. Leg hypertonia was associated with cPVL, regardless of age.

Interpretation: High-risk infants due to an early lesion of the brain often present with muscle tone impairment. In these infants, hypertonia and asymmetric muscle tone of the arms were from 7 months onwards associated with the diagnosis of CP at 21 months; hypertonia of the legs was not.

Shortened form of the title

Muscle tone impairments in high-risk infants

Keywords

- infancy
- muscle tone
- hypertonia
- hypotonia
- cerebral palsy

Abbreviations

CA	corrected age
CP	cerebral palsy
(c)PVL	(cystic) periventricular leukomalacia
GMFCS	Gross Motor Function Classification System
L2M0-2	LEARN2MOVE 0-2 years project
OR	odds ratio
TINE	Touwen Infant Neurological Examination
UMCG	University Medical Center Groningen

1. INTRODUCTION

Muscle tone regulation is one of the building blocks of motor control and therefore atypical muscle tone affects motor development.[1] Muscle tone is brought about by a constant feedback loop between the peripheral and central nervous system. When the feedback loop is interrupted, for example due to an early lesion of the brain, atypical muscle tone may occur.[2]

Atypical muscle tone is a key symptom in the diagnosis of cerebral palsy (CP).[3] However, it takes developmental time before the clinical picture of CP, including its atypical muscle tone, is established. The median age of diagnosis is 11 months and varies between 6 months and 5 years or later.[4] Infants at high risk of CP or other neurodevelopmental disorders may show atypical muscle tone that varies in type, severity and occurrence over time.[5,6] Recent guidelines recommend a combination of clinical tools for the early detection of CP, including neonatal magnetic resonance imaging (MRI), general movement assessment and a standardized infant neurological examination.[7] The latter is relevant since the diagnosis of CP is a clinical one, i.e., based on the clinical and neurological signs. In addition, it is important to realize that in the majority of infants at risk of neurodevelopmental disorders neonatal MRIs are lacking.[8]

Hypotonia in a single part of the body is rather prevalent in the general infant population.[9,10] Without other accompanying neurological signs, it has little clinical significance.[11] However, hypotonia present from birth onwards, and persisting hypotonia during infancy warrant clinical attention. Infants later diagnosed with CP, for example due to periventricular leukomalacia (PVL), may present with generalized neonatal hypotonia that gradually changes into hypertonia during the first year of life, mainly in the extremities.[10] In these infants, hypotonia in neck and trunk often persists throughout infancy.[12]

Hypertonia in infancy is less common. It raises clinical attention when present from birth onwards, as it may be an indicator of severe neurological pathology.[13] Probable causes are brain lesions, for example lesions of the cerebral cortex or white matter; lesions that are also risk factors for the development of CP.[13] However, infants who later get diagnosed with spastic CP often do not present with hypertonia in early life.[10,13,14] Hypertonia often emerges with increasing age.[12,15] In a Swedish registry population of children with CP, the prevalence of spasticity of the gastrocnemius muscle rose from 25% at 1 to 38% at 5 years of age.[16] In infants later diagnosed with unilateral CP hypertonia in the extremities on one side of the body generally emerges with increasing age.[12]

Knowledge on the early development of muscle tone impairments is scarce. Yet, such knowledge is needed to understand the development of spasticity, a core symptom of most children with CP. In addition, such knowledge is important information for family counselling.[8,17] To the best of our knowledge no studies exist that longitudinally assessed muscle tone impairments in infants with an early brain lesion. The LEARN2MOVE 0-2 years project (in short: L2M0-2) offered an opportunity to evaluate which developmental trajectories of atypical muscle tone are associated with CP at 21 months corrected age (CA). In L2M0-2, infants were assessed longitudinally with standardized neurological examinations during their first 21 months after term age. In these very high-risk infants we addressed the following questions: (1) What is the prevalence of specific types of atypical muscle tone, e.g., hypotonia of neck and trunk, hypertonia in the legs, or asymmetric muscle tone?; (2) Are specific types of atypical muscle tone associated with an increased risk of CP and if so, from which age onwards?; (3) Are specific types of atypical muscle tone associated with specific brain lesions, in particular cystic periventricular leukomalacia (cPVL), i.e., the brain lesion most strongly associated with CP,[18] and if so, is the association related to the infants' age at the neurological assessment?

2. MATERIALS AND METHODS

2.1. Study design and participants

This exploratory study is part of L2M0-2, a randomized controlled trial to evaluate the effect of two different forms of early intervention in infants at high risk of CP. Neurological outcome in both groups was similar.[19] Inclusion criteria of L2M0-2 were age at enrolment between 0-9

months CA and the presence of at least one of the following conditions: 1) cystic periventricular leukomalacia (cPVL); 2) parenchymal lesion of the brain; 3) neonatal hypoxic-ischaemic encephalopathy with brain lesions on MRI; and 4) neurological dysfunctions suggestive of development of CP. Infants with severe congenital disorders or having caregivers with insufficient comprehension of the Dutch language were excluded. Forty-three infants were included between 2008 and 2013.[19] L2M0-2's study design was approved by the Medical Ethical Committee of the University Medical Center Groningen (METc 2008.176) and registered in the Dutch trial register (NTR1428). Parents gave informed consent.

2.2. Brain imaging

All infants underwent neonatal brain imaging (mostly MRI) as part of standard clinical care (see Table 1). An experienced paediatric neurologist blinded to clinical data classified brain imaging data based on the predominant pattern: a) periventricular leukomalacia (PVL; cystic and non-cystic), b) cortical infarction (full-term border-zone infarction or middle cerebral artery infarction), c) posthaemorrhagic porencephaly, d) basal ganglia or thalamic lesions, and e) non-specific lesions (e.g., ventriculomegaly) or no lesions.[20]

2.3. Neurological assessment

Infants were assessed five times: at inclusion (T0), after 3 (T1), 6 (T2), and 12 (T3) months, and at 21 months CA (T4). For some infants, T3 and T4 coincided. Infants with four or five neurological assessments during the study period were included in the current study (n=39). For descriptive purposes, the assessment moments were reclassified into the following (corrected) age categories: i) 0-3 months (n=29); ii) 4-6 months (n=36); iii) 7-9 months (n=35); iv) 10-12 months (n=19); v) 13-17 months (n=28); and vi) 18-22 months (n=38), resulting in a total of 185 neurological assessments. If infants had two assessments within one age category (n=4), only the assessment performed at the oldest age was included into the descriptive analyses.

At each time point, infants were neurologically assessed with the Touwen Infant Neurological Examination (TINE).[21] TINE is one of the standardized infant neurological assessments with good psychometric properties, including a good reliability (inter-assessor agreement $\kappa = 0.83$, 95% CI 0.68–0.99).[21] Its validity has been established in term and preterm infants, which makes it suitable for the neurological evaluation of infants at risk of neurological disorders with different aetiologies.[21] According to TINE, muscle tone was assessed by evaluating resistance to passive movements in each of the following body parts separately: neck/trunk, arms, legs, and ankles. Muscle tone was reported as i) typical, or atypical: ii) hypotonia; iii) hypertonia; or iv) changing tone, the latter indicating a varying muscle tone. In case of asymmetry between left and right extremity, its presence was recorded and muscle tone of the worst side was assigned in the analyses. At the final assessment (18-22 months CA) the diagnosis of CP was made based on the TINE. In infants diagnosed with CP, motor function was classified using the Gross Motor Function Classification System (GMFCS).[22] In infants without CP neurological condition was assessed with the Hempel examination.[23] This standardized assessment focuses on the presence of minor neurological dysfunction (MND), i.e., neurological dysfunction without evident neurological pathology, such as CP. The Hempel examination evaluates signs in five domains of function: fine motor function, gross motor function, posture and muscle tone, reflexes and visuomotor function. When domain specific criteria are met, a domain is classified as atypical. Children are classified as neurologically normal when none of the domains is atypical, as simple MND (sMND) when one domain is atypical and complex MND (cMND) when more than one domain is atypical.[24] sMND represents a non-optimal but normal brain function, whereas cMND is considered the clinically relevant form of MND, since it is clearly associated with perinatal adversities, and learning and behavioural problems.[25]

2.4. Statistical analyses

Muscle tone was dichotomized into hypertonia and other muscle tone (see results section). Type of brain lesion was dichotomized into present or absent cystic PVL (cPVL). Descriptive

statistics were performed with SPSS, version 26. Generalized linear mixed effects model analyses, including all assessments at their exact CA's, were performed to evaluate associations between the developmental trajectories of those muscle tone patterns that showed most clear associations with CP in the univariable analyses, and CP and cPVL, using R version 3.6.3.[26] Random subject effects were incorporated to account for repeated assessments within an infant. Fixed effects were included for time (age), group (CP versus no CP, and cPVL versus non-cPVL) and interaction between age and group. From these subject specific models, time profiles were created describing the average developmental trajectory of the muscle tone impairment per group. Using these profiles, the earliest age was calculated at which the difference between the groups became statistically significant. P-values <0.05 were considered statistically significant.

3. RESULTS

3.1. Background characteristics

Background characteristics of the study group are shown in Table 1. The high-risk nature of the group is reflected by a median gestational age of 30.9 weeks, with almost 75% infants born preterm (< 37 wks). The most prevalent brain lesions were posthaemorrhagic (n=10) porencephaly and cystic PVL (n=9; Table 1). At 21 months CA, 20 infants (51%) were diagnosed with CP; 19 (49%) were not. The 20 infants with CP had spastic CP; 5 of them had unilateral CP, 15 had bilateral CP. The majority of children without CP (11/19) were diagnosed with cMND.

3.2. Prevalence of atypical muscle tone in the various body parts

The neurological vulnerability of the study group was reflected by the high prevalence of atypical muscle tone: in 172 out of the 185 assessments (93%), infants had an atypical muscle tone in three or four body parts (Figure 1). We observed a high heterogeneity in muscle tone patterns throughout infancy (45 different patterns; Supplementary Material S1).

In the neck and trunk, hypotonia was the most frequently observed muscle tone impairment. Its prevalence varied between 93% at 0-3 months (27/29) and 68% at 10-12 months (13/19). In the arms, hypertonia was the most frequently observed deviation in muscle tone. Its prevalence decreased with increasing age from 76% at 0-3 months (22/29) to 35% at 18-22 months (13/38). In the legs, hypertonia was the most frequently observed muscle tone impairment up to and including 17 months. Its prevalence decreased from 86% at 0-3 months (25/29) to 39% at 13-17 months (11/28). At 18-22 months, hypotonia was the most frequently observed muscle tone impairment in the legs with a prevalence of 47% (18/38). In the ankles, hypertonia was the most frequently observed impairment in muscle tone, fluctuating between 91% at 7-9 months (32/35) and 63% at 18-22 months (24/38).

The most frequently observed muscle tone pattern in the total of 185 assessments was hypotonia of the neck and trunk in combination with hypertonia of arms, legs and ankles (28%). Its prevalence decreased with increasing age: from 62% at 0-3 months CA (18/29) to 8% at 18-22 months CA (3/38).

Inspection of the raw data presented in Figure 1 indicates that hypotonia in neck and trunk, whether or not in combination with hypertonia of the extremities, continued to be highly prevalent in all infants, therewith not differentiating between children later diagnosed with CP or not. The figure also indicates that hypertonia was the most prevalent muscle tone classification in the extremities and that this might be associated with the diagnosis of CP. We therefore analysed the developmental changes in the prevalence of hypertonia in the extremities in more detail, including their associations with CP and brain lesion.

3.3. Hypertonia in the extremities and CP

3.3.1. *Upper extremities*

Univariable analysis showed that the presence of arm hypertonia at 0-3 months CA was not associated with development of CP at 21 months CA: ten out of the 22 infants (45%) with hypertonia of the arms developed CP, while 57% (4/7) of the infants without hypertonia did

develop CP (Figure 1; p=0.458). At 18-22 months, hypertonia of the arms was associated with CP: infants with hypertonic arms had a significantly higher prevalence of CP than the infants without hypertonia (100% vs 29%, p<0.001). The mixed effects models indicated that the developmental trajectories of infants who were and were not diagnosed with CP, started to differ at 7 months CA (OR 1.23, 95%CI 1.08 – 1.42; Supplementary Material S2). This means that from 7 months CA onwards, infants later diagnosed with CP had a significantly higher prevalence of hypertonia in the arms than infants without CP (Figure 2A). We paid special attention to asymmetries in arm muscle tone. Their prevalence varied between 10% (3/29) at 0-3 months to 34% (12/35) at 7-9 months. Further inspection of the data indicated that at 4-6, 7-9, 13-17, and – not surprisingly – at 18-22 months, unilateral arm hypertonia was associated with the diagnosis of unilateral CP (Table 2).

3.3.2. Lower extremities

Univariable analysis showed that 13 infants (52%) of the 25 presenting with hypertonic legs at 0-3 months CA were later diagnosed with CP, while 1 of the 4 infants without hypertonia developed CP. In the infants with hypertonic legs at the age of 18-22 months, 78% (7/9) had CP, while 45% (13/29) of the infants without hypertonic legs was diagnosed with CP. At both time points, the presence of hypertonia was not significantly associated with CP (p=0.598 and 0.130, respectively). The mixed effects models also showed that there was no significant difference in probability of hypertonic legs between infants who were and were not diagnosed with CP (OR 2.16, 95%CI 0.99-5.08) (Supplementary Material S2). The prevalence of an asymmetry in leg muscle tone decreased from 48% at 0-3 months (14/29) to 18% at 18-22 months (7/38). The asymmetries were not associated with a later diagnosis of unilateral CP (Table 2).

Figure 1 shows that 48% (12/25) of the infants with hypertonic ankles at 0-3 months CA developed CP, whereas 50% (2/4) of the infants without hypertonia did (p=1.000). Seventy-five percent (18/24) of the infants with hypertonic ankles at 18-22 months CA were diagnosed with CP, whereas 14% (2/14) of the infants without hypertonic ankles were. This difference was statistically significant (p=0.001). Yet – as Figure 1 illustrates – at none of the younger ages was hypertonia in the ankles associated with CP. The prevalence of an asymmetry in ankle muscle tone fluctuated between 42% at 10-12 months (8/19) and 18-22 months (16/38), and 63% at 7-9 months (22/36). Only at the age of the diagnosis of CP, unilateral CP was associated with a unilateral ankle hypertonia (Table 2).

3.4. Hypertonia in the extremities and cPVL

The mixed effects models indicated that the prevalence of hypertonic arms in infants with cPVL resembled that of infants without cPVL (OR 1.58, 95%CI 0.409-6.28) (Supplementary Material S2).

The mixed effects models indicated that from the earliest assessment age onwards hypertonia in the legs was more frequently found in infants with cPVL than in infants without cPVL (OR 2.61 (95%CI 1.03 – 7.16) (Supplementary Material S2). This difference did not change with increasing age, also shown by the more or less parallel lines in panel B of Figure 2. Univariable analysis indicated that at none of the assessment ages cPVL was associated with ankle hypertonia. For instance, at 0-3 months, seven out of eight infants (88%) with cPVL had hypertonia in the ankles and 18 out of 21 infants (86%) without cPVL (p=1.000). At 18-22 months, 89% (8/9) of the infants with cPVL had hypertonia in the ankles, versus 55% (16/29) of the infants without cPVL (p=0.115).

4. DISCUSSION

The current study showed that infants at very high risk of a neurodevelopmental disorder – mostly due to a lesion of the brain – had a high prevalence and wide diversity of muscle tone impairments throughout infancy. The most prevalent muscle tone pattern was the combination of hypotonia of neck and trunk and hypertonia in the extremities occurring both in children with and without CP. During the first half year of life prevalence of specific types of muscle tone impairment did not differ between infants who were and who were not diagnosed with CP.

From 7 months onwards, hypertonia in the arms was associated with CP. Asymmetrical arm muscle tone was associated with unilateral CP. Additionally, infants with cPVL had throughout infancy a higher prevalence of hypertonia in the legs than infants without cPVL.

Our data illustrate that some infants outgrow their initial muscle tone impairment, which is in line with the study of Chaudhari and coworkers, who reported a decreasing prevalence of muscle tone impairment during the first year in a mixed group of infants at risk.[27] The normalization of muscle tone could be a sign of full functional recovery of the nervous system or a transient phase in the development of other neurodevelopmental impairments, such as learning or behavioural disorders.[28] Nonetheless, in many children with an early brain lesion the muscle tone impairments persisted; around 21 months the large majority of children were diagnosed with CP or cMND, which included the presence of impaired muscle tone.

In our high-risk infants, muscle tone impairments during the first half year post-term had a high prevalence but did not predict CP. This may explain why a traditional neurological examination that pays relatively much attention to muscle tone, such as the Hammersmith Infant Neurological Examination[29] or the Amiel-Tison examination[30], does predict CP in early infancy less well than general movement assessment.[31] It is well-known that early prediction of CP is best on the basis of an MRI at term age and a general movement assessment around 3 months CA.[7,8] In older infants a standardized neurological assessment, such as HINE, is recommended.[7,8] This does not mean that we should not evaluate muscle tone at early age: muscle tone assessment remains an integral and important part of the neurological examination. Our results, however, do underline that it takes developmental time before neurological signs become specific.[8]

In our study, hypertonia in the arms was from 7 months onwards associated with CP and asymmetric arm muscle tone with unilateral CP. It is well known that in unilateral CP, increased muscle tone manifests especially in the arm.[15] The infants with asymmetric arm muscle tone had shown unilateral hypertonia as a precursor of unilateral CP. This means that part of the infants with unilateral CP contributed to the association between hypertonia in the arms and CP. Nonetheless, they were not entirely responsible for the association (Figure 1). Our results are in line with those of Ryll and colleagues, who recently reported that prediction of unilateral CP in infants with a specific high risk for unilateral CP on the basis of arm-hand activities can be reliably done from 3.5-4.5 months CA onwards, and that its diagnostic accuracy increases with increasing age.[32]

Muscle tone impairment in the lower extremities during infancy did not predict CP; only at the age of the diagnosis of CP hypertonia in the ankles was significantly associated with CP. Figure 1 shows that both infants with unilateral and bilateral CP contributed to this association. Muscle tone in the legs was not associated with CP. Our findings may be explained by the size of the cortical motor areas contributing to motor control of each of the three body parts: the area involved and its descending corticospinal projections in the control of arm movements is larger than that involved in control of the ankle and foot, which in turn is larger than that in charge of the leg.[33]

Our results also indicated that infants with cPVL had a higher prevalence of hypertonic legs than infants without this brain lesion, regardless of age. cPVL is a white matter lesion of the preterm brain that interferes with functioning of the corticospinal tract.[34] Damage of the white matter near the posterior parts of the lateral ventricles typically affects the motor fibres to the lower extremities.[15] This may explain why we did not find an association between cPVL and hypertonia in the arms. Despite the association between cPVL and hypertonia in the legs, hypertonic legs did not predict CP.

To the best of our knowledge, this is the first study describing the development of muscle tone in different body parts in infants at high risk of neurodevelopmental disorders and its association with CP. The study's major strength is the longitudinal data collection using a reliable infant neurological assessment: all infants were assessed at least four times throughout infancy. Additionally, information was available on neonatal brain imaging which enabled us to investigate possible relations between atypical muscle tone and cPVL. A limitation of the current study is the small size of the study group, implying that the results cannot be generalized. The brain imaging data were obtained as part of clinical practice, which

in the Netherlands includes for infants at very high risk an MRI-scan. Worldwide MRI-scans are not always available for infants; in these situations, repeated neonatal cranial ultrasound scans form an adequate alternative to detect the infant's brain lesions.[35] In our study, the large heterogeneity in brain lesions and muscle tone patterns hampered subgroup analyses, for example exploration of muscle tone development in children with other brain lesions than cPVL (see Supplementary material S1). The study's small sample size also implies that the findings of the study cannot be generalized.

5. CONCLUSION

Our study underlines the importance of documenting development of atypical muscle tone as part of a standardized neurologic assessment, since it assists the prediction of CP. The study indicated that hypertonia in the arms is in high-risk infants from 7 months onwards associated with an increased risk of CP, and that asymmetric arm muscle tone is an early marker of unilateral CP. Hypertonia in the arms, either unilateral or bilateral, thus may serve early detection of CP and providing infants and families with proper early intervention.

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Table 1 Background characteristics

	total (*n*=39)
sex (girls/boys), *n*	15 / 24
gestational age, weeks (median + range)	30.9 (25.9 - 41.4)
preterm birth (GA < 37 weeks), *n* (%)	28 (72)
birth weight, grams (median + range)	1788 (720 - 5400)
neonatal brain imaging, *n*	
MRI / cranial ultrasound	33 / 6
type of brain lesion, *n* (%)	
periventricular leukomalacia	13 (33)
cystic	9 (23)
non-cystic	4 (10)
cortical infarction	3 (8)
posthaemorrhagic porencephaly	10 (26)
basal ganglia / thalamic lesion	6 (15)
no / nonspecific lesion	7 (18)
neurological outcome at 21 months CA, *n* (%)	
no CP	19 (49)
typical	1 (3)
sMND	5 (13)
cMND	11 (28)
no Hempel assessment	2 (5)
CP	20 (51)
unilateral / bilateral	5 / 15
GMFCS I / II / III / IV / V	3 / 7 / 4 / 3 / 3

Table 2 Associations between asymmetrical muscle tone and unilateral CP

		ARMS			LEGS			ANKLES		
		uni	no CP	*p*-value	uni	no CP	*p*-value	uni	no CP	*p*-value
0-3 mo	asym	0	1	1.000	0	8	0.471	1	8	1.000
	no asym	2	14		2	7		1	7	
4-6 mo	asym	3	5	**0.036***	0	6	0.526	2	11	1.000
	no asym	0	14		3	12		1	8	
7-9 mo	asym	4	4	**0.039***	3	4	0.274	5	11	0.266
	no asym	1	13		2	13		0	6	
10-12 mo	asym	2	1	0.055	0	2	1.000	0	2	0.109
	no asym	0	8		2	7		2	7	
13-17 mo	asym	3	1	**0.044***	3	4	0.326	4	8	0.615
	no asym	2	12		2	9		1	5	
18-22 mo	asym	3	1	**0.012***	2	2	0.135	4	6	**0.029***
	no asym	1	16		2	16		0	12	

This table is a compilation of small cross-tables (3rd / 5th / 7th column) that provide the raw numbers of infants with asymmetrical muscle tone in the various parts of the body and various ages. The crosstabs show the numbers of infants with and without asymmetrical muscle tone (presented in the rows) and the later diagnosis of unilateral CP or no CP (presented in the columns). Note that the table only includes the children with unilateral CP or no CP.
P-values are based on the Fisher's exact test. Significant associations in bold: * $p<0.05$.
Asym: asymmetry. No asym: no asymmetry. Uni: unilateral CP.

Supplementary material S1 **Muscle tone findings per infant and brain lesion**

			muscle tone pattern per assessment				
infant ID	**brain lesion**	**neurological outcome**	**1**	**2**	**3**	**4**	**5**
1	cPVL	bi CP	4333	2333	2333	4333	4444
2	cPVL	bi CP	2333	2443	2233	2443	2423
3	cPVL	bi CP	2333	4333	3333	2444	2433
4	cPVL	bi CP	2333	2343	2333	2333	2443
5	cPVL	bi CP	2433	2443	2222	2343	2223
6	cPVL	bi CP	2333	2333	2443	2333	-
7	cPVL	bi CP	2333	2333	2343	3333	2333
8	cPVL	bi CP	2444	2333	2333	2333	1333
9	cPVL	bi CP	2133	2333	2333	2313	2323
10	CI	uni CP	2333	2323	2323	2313	-
11	CI	uni CP	2333	2323	2333	2333	2313
12	CI	bi CP	2313	2223	2221	2241	2223
13	PP	bi CP	2333	2333	3333	2333	2333
14	PP	uni CP	2333	2343	2323	2222	2333
15	PP	uni CP	2333	2313	1333	2333	-
16	PP	uni CP	2343	2323	2433	1323	-
17	PP	bi CP	2333	4333	2344	2343	-
18	PP	cMND	2333	1333	1222	2433	2113
19	PP	cMND	2333	2333	2113	2221	2123
20	PP	cMND	1122	2333	2222	2141	-
21	PP	cMND	2233	2333	1333	1333	2122
22	PP	missing	2442	2313	2443	1333	-
23	BG/T	bi CP	2333	2333	2323	2323	-
24	BG/T	bi CP	4131	2122	2322	2133	2322
25	BG/T	cMND	2333	2343	2323	2323	2x22
26	BG/T	cMND	2333	2243	4222	2221	2222
27	BG/T	cMND	2343	2323	2333	2223	1113
28	BG/T	sMND	2333	4322	2143	2243	2222

29	n-cPVL	bi CP	2333	4333	2333	2243	2423
30	n-cPVL	cMND	2333	2323	2143	2223	2223
31	n-cPVL	cMND	2333	4333	2133	2433	2222
32	n-cPVL	cMND	2433	2122	2133	2121	-
33	n/n.s.	cMND	2433	2221	2223	1333	2223
34	n/n.s.	cMND	2333	2113	1133	2222	2211
35	n/n.s.	sMND	4344	2321	2323	2222	-
36	n/n.s.	sMND	3333	4333	1323	2123	2234
37	n/n.s.	sMND	2433	2333	1313	2233	2433
38	n/n.s.	sMND	2333	2431	2433	1313	2111
39	n/n.s.	typical	2333	4333	2333	2113	1111

Legend to the table:

The colored number codes represent the muscle tone patterns per assessment. The first number in the code represents the muscle tone classification in neck/trunk, the second in arms, the third in legs, and the fourth in ankles. The green 1's represent typical tone, the red 2's hypotonia, the red 3's hypertonia and the blue 4's changing tone. For example: 2343 represents the pattern with hypotonia in neck/trunk, hypertonia in arms, changing tone in legs, and hypertonia in ankles.

cPVL: cystic periventricular leukomalacia. CI: cortical infarction. PP: posthemorrhagic porencephaly. BG/T: basal ganglia / thalamus lesion. n-cPVL: non-cystic periventricular leukomalacia. n/n.s.: no / non-specific lesion. uni: unilateral. bi:bilateral.

Supplementary material S2 Generalized mixed effect model analyses: associations between hypertonia and CP and cPVL

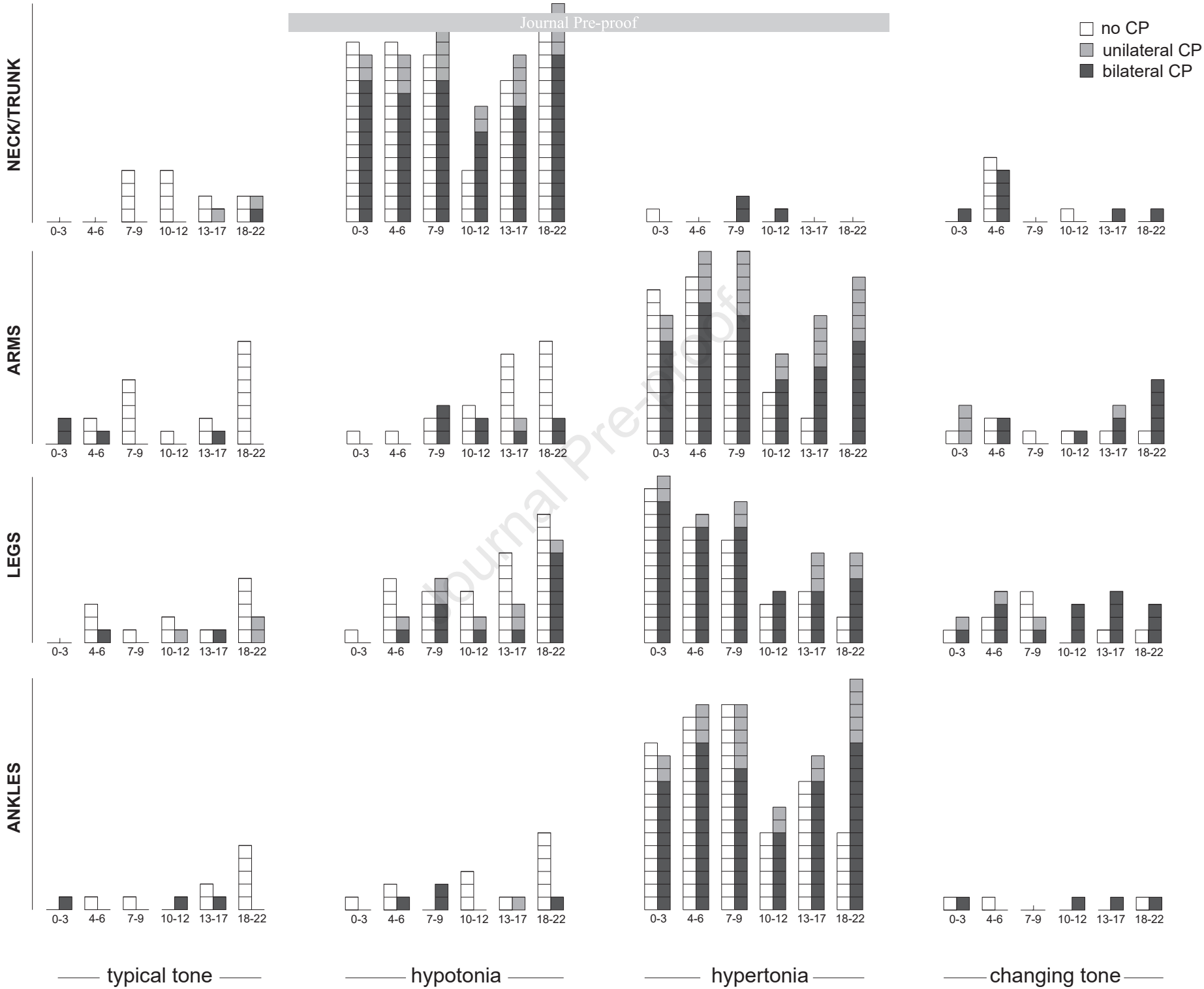
	variables in model	fixed effects (β)	OR (exp(β)) (95% CI)		age difference (months)
hypertonia arms	intercept	**2.170*** **	8.76	(2.891 – 32.76)	≥ 7.0
	age	**-0.257*** **	0.773	(0.681 – 0.856)	
	CP	-0.344	0.709	(0.140-3.560)	
	CP*age	**0.205** **	1.23	(1.082-1.42)	
	intercept	**1.85*** **	6.34	(2.67 – 18.0)	*none*
	age	**-0.133*** **	0.875	(0.820 – 0.927)	
	cPVL [a]	0.459	1.58	(0.409 – 6.28)	
hypertonia legs	intercept	**0.959***	2.61	(1.00 – 3.61)	*none*
	age	**-0.137*** **	0.872	(0.822 – 0.919)	
	CP [a]	0.772	2.16	(0.998 – 5.08)	
	intercept	**1.10** **	3.01	(2.67 – 18.0)	≥ 0 [b]
	age	**-0.134*** **	0.875	(0.824 – 0.922)	
	cPVL [a]	**0.958***	2.61	(1.03 – 7.16)	

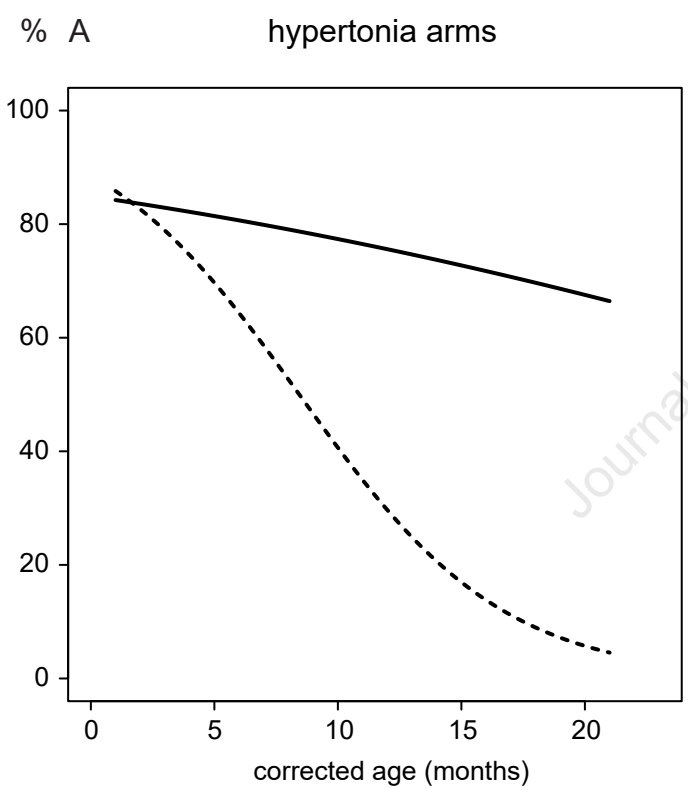
Summary of the variables that were and were not associated with hypertonia in the arms and legs in the generalized mixed effect model analyses. The intercept indicates the mean value of the chance of hypertonia when the other variables are 0. CP*age denotes the statistical interaction between CP and age.
Significant effects of variable in bold: * p<0.05, ** p<0.01, *** p<0.001.
Exp (β) is presented here as odds ratio (OR): it represents the growth factor of the developmental trajectory. For age it reflects the growth factor per month. The most right column presents the age at which the estimated mean starts to differ between the groups (CP vs no CP, cPVL vs non-cPVL).
[a] The interaction term was not statistically significant in this model and therefore not presented in the table.
[b] There is a constant, age-independent significant difference in the proportion of infants with hypertonic legs between the group with cPVL and the group without.
CP: cerebral palsy. cPVL: cystic periventricular leukomalacia. OR: odds ratio.

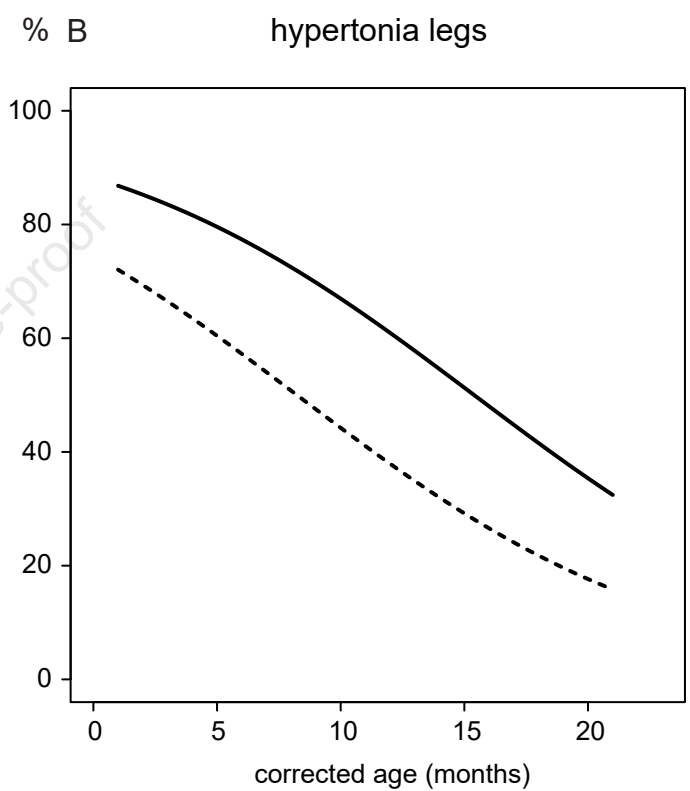
Legends to the figures

Figure 1 Prevalence of atypical muscle tone in various body parts across infant age in relation to diagnosis of CP
The figure illustrates the prevalence of atypical muscle tone per body part (on the rows) and per type of muscle tone impairment (in the columns) at the various assessment ages (0-3; 4-6; 7-9; 10-12; 13-17; 18-22 months CA). Each box represents one assessment: the white boxes present the infants without CP, the light grey boxes the infants with unilateral CP, and the dark grey boxes those with bilateral CP.

Figure 2 Development of hypertonia in arms and legs of infants with and without CP or cPVL
Average developmental trajectories of A) of infants with hypertonia in arms in relation to the diagnosis of CP, and B) of infants with hypertonia in the legs in relation to the presence of cPVL. The x-axes present (corrected) age in months; the y-axes the percentage of infants showing hypertonia in either arms or legs. The continuous lines present trajectories of infants diagnosed with CP or cPVL, respectively. The dotted lines show trajectories of infants without CP or without cPVL, respectively.







Highlights

- High-risk infants have a high prevalence of muscle tone impairments (>90%)
- Axial hypotonia with limb hypertonia is most common pattern in high-risk infants
- From 7 months onwards arm hypertonia was associated with CP
- Asymmetrical muscle tone of the arms was associated with unilateral CP
- Hypertonia of the legs was associated with cPVL

Conflict of interests

No conflicts of interests. See attached files.